Attachment B: Literature Review

Author / Title / Journal / Year	Type of Study	Outcomes Studied	Patient Characteristics	Results	HCFA Comments
Al-Momen AK, Huraib S, Mitwalli A, et al / Intravenous iron saccharate in hemodialysis patients receiving r-HuEPO / Saudi Journal of Kidney Diseases and Transplantation / 1994	Cohort study	Effects of erythropoietin therapy (EPO) and intravenous (IV) iron (Fe) saccharate were assessed using hemoglobin (Hb), hematocrit (Hct), serum iron, serum ferritin (SF), and total iron binding capacity (TIBC) as primary endpoints.	109 hemodialysis (HD) patients were enrolled into the study. All were treated with EPO therapy for a minimum of 8 weeks. Patients who were iron deficient were given 100 units/kg of EPO. Patients who were not iron deficient were given 50 units/kg of EPO. Patients that were excluded from the study had active bleeding, hemoysis, inflammation, infection, or malignancy. Patients were divided into 2 treatment groups. Group 1 (n=58) received high dose IV Fe (500mg). Group 2 received low dose IV Fe (100mg).	Group 1 had 42 iron deficient patients and 16 non-iron deficient patients. Group 2 had 22 iron deficient patients and 29 non-iron deficient patients. All patients from both groups showed statistically significant increase in Hct, Hb, TIBC, SF levels at the 4th week of IV Fe administration. EPO doses for the iron deficient patients were also lowered to 50 units/kg. Group 1 experienced adverse effects in 9 patients. None were reported in Group 2.	Study provides data on the dose-related effectiveness of IV Fe saccharate. There was no description on how sample groups were divided; lack of randomization may introduce selection bias. Furthermore, analysis made no mention of how distinctions were made between iron deficient vs. non-iron deficient. Authors state patients with functional iron deficiency were excluded, though they did not elaborate how. No comparisons were made to oral iron.

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Allegra V, Mengozzi G, Vasile A / Iron deficiency in maintenance hemodialysis patients: assessment of diagnosis criteria and of three different iron treatments / Nephron / 1991	Cohort study	SF levels were assessed. Relationship between changes in SF levels and response to iron treatment was evaluated. Positive response to treatment was defined to be an increase of at least 15% in Hb and Hct levels compared to baseline. It was postulated that a positive response is indicative of iron deficiency.	SF levels in 250 healthy volunteers were evaluated in order to determine a 95% percentile range. 72 patients on maintenance HD were divided into 3 groups according to their SF baseline value: Group A = >191, Group B = 19-191 Group C = <19 Each group was further divided into 3 treatment groups: Oral 1 = Oral Fe-ferritin Oral 2 = Oral Fe-condroitin sulfate IV Fe = IV Fe gluconate (Ferrlecit) 7 patients were excluded from the study due to hemorrhages, transfusions, or hepatitis. 9 patients moved between treatment groups	From the 250 volunteers, a normal SF range was developed (19-191 ng/ml). In patients with SF levels <191, the IV Fe treatment had positive response rates significantly higher then both oral treatments. A B C Oral 1 0/5 2/10 1/7 Oral 2 0/5 1/6 3/7 IV Fe 0/7 5/11 10/16 Patients with SF levels >191 (Group A) did not show positive response to any iron treatment. Authors concluded that IV Fe therapy was the optimal treatment of choice for iron deficiency.	Study contains small sample sizes. Treatment groups ranged in size from 5 to 16 patients. In addition, there were no descriptions on how patients were divided into treatment groups. There is cause for concern regarding the movement of patients between treatments groups or out of the study. There is little information on the 250 volunteers to validate the reliability of the normal ranges of SF levels. Study gives no indication on EPO use, an important factor since EPO is a significant stressor on iron regulation.

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Anastassiades E, Howarth D, Howarth J, et al / Monitoring of iron requirements in renal patients on erythropoietin / Nephrology Dialysis Transplantation / 1993	Cohort study	Hb, SF, TSAT, serum iron, and TIBC were monitored during the course of treatment.	38 patients were enrolled into the study. 9 were on HD, 18 on continuous ambulatory peritoneal dialysis (CAPD) and 11 had advanced renal failure but did not yet need dialysis. All patients were given EPO. Patients without iron overload (SF levels < 500 prior to treatment) were given 300 mg of elemental iron/day (orally). Patient with iron overload were not given iron supplements unless SF level fell below 200. Patients unable to take oral iron were given IV Fe dextran (n=4).	At 12 weeks: Pre Post All pts. Hb 6.93 10.39* Overloaded Hb 6.47 9.85* Non - Overload Hb 7.04 10.70* HD patients achieved a significantly lower Hb than CAPD patients (9.4 vs. 10.99 g/dl). Pre-dialysis patients did not differ from the other two groups. SF levels declined significantly in all groups. TSAT did not differ in any group.	In the study patients experienced an increase in Hb levels while on EPO and oral iron. Authors state that oral iron is sufficient to supply iron for erythropoiesis and restore body iron stores. However, the aggregate data does not distinguish between patients receiving oral iron and those receiving IV Fe dextran. In addition, the observed decline in SF levels is inconsistent with the authors' conclusions.
Andrews N / Disorders of iron metabolism / New England Journal of Medicine / 1999	Overview	Not a clinical trial.	Not a clinical trial.	Not a clinical trial.	Article provides background information on the physiology of iron transport and various diseases of iron deficiency. No direct clinical evidence is presented.
Bailie G, Johnson C, Mason N / Parenteral iron use in the management of anemia in end-stage renal disease patients / American Journal of Kidney Diseases / 2000	Overview	Not a clinical trial.	Not a clinical trial.	Not a clinical trial.	Article provides a comparative review of the available literature on the safety, toxicity, and clinical effectiveness of three IV Fe agents: iron dextran, iron sucrose, and iron gluconate.

Author / Title / Journal / Year	Type of Study	Outcomes Studied	Patient Characteristics	Results	HCFA Comments
Bergmann M, Grutzmacher P, Heuser J, Kaltwasser J / Iron metabolism under rEPO therapy in patients on maintenance hemodialysis / The International Journal of Artificial Organs / 1990	Case series	Study evaluates the long-term course of SF, serum iron, TIBC, and Hct as patients are undergoing EPO therapy. The effects of iron substitution on these parameters were also assessed.	18 non-transfused patients on regular HD with Hct below 26% were treated with EPO and enrolled in the study. Patients were randomly assigned to 3 different EPO dose groups (40, 80, 120 units/kg body weight, 3 times per week). 2 patients were excluded from evaluation because of kidney transplantation and development of hepatitis. 9 out of the 16 patients were on regular iron substitution (7 on oral, 2 on IV [agent not identified]) prior to the study.	During EPO therapy, Hct levels rose in all patients. At the end of the correction phase, mean Hct rose from 22.9% (+/- 2.1) to 33.7% (+/- 1.4). The rate of increase of Hct was dose dependent. Mean SF levels dropped from 203 micrograms/l (+/- 124) to minimum of 71 (+/- 59) during the correction phase and was at 102 (+/- 76) after 6 months. Changes in serum iron and TIBC were moderate. 5 of 7 seven patients not on iron therapy before EPO were started on treatment because initial Hct increase did not continue.	Results are based largely on observational data on the effects of EPO on SF, serum iron, TIBC, and Hct levels. The study shows a sharp decrease in SF levels which corresponds to an increase in Hct levels. The aggregate data however does not separate out the differences between patients on iron therapy vs. those who were not. The sample size is quite small. The study does not speak to the effectiveness of iron therapy on the treatment of iron deficiency in HD patients.
Canavese C, Grill A, De Constanzi E, Martina G, Buglione E, Valente D, et al / How to save money for erythropoietin therapy by changing from 'roller coaster' to continuous iron supplementation / Nephron / 1999	Case series	For a 6-month period, EPO dose was compared to Hb, iron, transferrin, transferrin saturation (TSAT), and SF levels in a sequentially untreated and then treated group.	40 stable HD patients who had maintained their target Hb levels using EPO were evaluated for 3 months while on continuous low-dose IV Fe gluconate (Ferrlecit) supplementation after a 3-month period in which iron therapy was unavailable.	During the period of IV Fe administration, EPO dose began steadily decreasing and 15 patients were allowed to stop EPO therapy. Hb levels remained steady or improved in face of decreases in EPO dosage.	This study does not compare treatment with a control. Article presents persuasive evidence suggesting a relationship between the effectiveness of EPO therapy and iron therapy. No comment was made on the effectiveness of injectable iron as a mode of iron supplementation.

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Dunea G, Swagel M, Bodiwala U, Arruda J / Intradialytic oral iron therapy / International Journal of Artificial Organs / 1994	Case series	Hct, SF, and TSAT levels were assessed. Compliance, refusal to treatment, and side effects were noted.	Part 1: (May 1990 - July 1991) 125 HD patients on fixed doses of EPO were given two ferrous sulfate tablets at the beginning dialysis session and two at the end. Dialysis sessions occurred 3 times per week. Responders were defined to be those patients showing an increase in Hct levels Part 2: (Oct 1992 - Jan 1993) 24 patients who had received intradialytic oral iron therapy were given IV Fe dextran Part 3: (Aug 1993) 124 patients were given 3 ferrous sulfate tablets some stage during their HD session. Responders were defined as those patients achieving a Hct of 30% or greater	Part 1: 12 patients (9.6%) refused oral iron treatment and were thus excluded. 30 patients were also excluded because of death or intercurrent illness. For the remaining 73 patients, 50 patients responded (68%) and 23 failed to respond (32%). The following were the Hct distributions: Hct. % of Group > 30%, 42% 28% - 30% 28% < 28% 30% Part 2: The following were the pre/post group distributions by Hct levels. Hct Pre Post > 30% 33% 58% > 28% 54% 83% 21 patients responded with an increase in Hct. 3 patients had a decrease in Hct. Part 3: 10% of patients refused treatment. 56 patients (52%) were responders, achieving Hct of 33.1% +/- 0.3%. Non-responders (48%) achieved Hct of 26.2%.	The study is largely an observational, uncontrolled study that monitored patients undergoing dialysis as IV Fe dextran became temporarily unavailable and later as reports of anaphylaxis began emerging. Method of oral administration (intradialytic) was not standard medical practice. The refusal of some patients to treatment may have affected the results since patients who were not able to tolerate oral iron would most likely refuse to undergo treatment. However, under ideal circumstances, around 42% - 52% of patients on oral iron will achieve Hct > 30%. 58% of patients on IV Fe therapy responded to treatment. It is important to note that the sample of patients observed during administration of IV Fe was considerably smaller than the other 2 sample populations. Results from these sample populations may not be easily compared to each other.

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Faich G, Strobos J / Sodium ferric gluconate complex in sucrose: safer intravenous iron therapy than iron dextrans / American Journal of Kidney Diseases / 1999	Retrospective analysis of market data	Safety of IV Fe gluconate complex (Ferrlecit) was compared to IV Fe dextran using adverse reaction rates and case-fatality rates .	Adverse event reports from the World Health Organization (WHO) were used to assess adverse reactions. Manufacturers of the iron products were contacted to estimate the number of units sold annually.	-- 3.3 allergy episodes per million doses sold for sodium ferric gluconate. -- 8.7 allergy episodes per millions doses sold for iron dextran. IV Fe gluconate had a substantially lower case fatality rate compared to Fe dextran (0 vs. 15.8%).	While the absolute number of episodes reported suggests a distinction, as a portion of the number of doses administered the difference is miniscule (0.0000033 vs. 0.0000087). The study does not address clinical effectiveness of one product compared to the other.
Fishbane S, Frei G, Maesaka J / Reduction in recombinant human erythropoietin doses by the use of chronic intravenous iron supplementation / American Journal of Kidney Diseases / 1995	Randomized clinical trial	Hct, SF, iron saturation, TSAT, and EPO dosage were monitored regularly during the 4 month study.	The study examined patients who met the following requirements: on HD for at least 3 months, receiving EPO and oral iron therapy for at least 3 months, no prior treatment with IV Fe dextran for at least 6 months, mean baseline SF greater than 100 ng/m, and TSAT greater than 15%. Out of the 107 patients meeting these criteria, 80 were randomly selected. Patients were randomly assigned to receive either IV Fe dextran (n=25) or continue on oral iron therapy (n=50).	23 patients were withdrawn during the course of the study; five in the IV Fe dextran group and 18 in the oral group. At 1 month and all subsequent months, mean Hct levels were significantly higher in the IV Fe group compared to the oral group. At 2 months and all subsequent months, mean EPO doses were significantly lower in the IV Fe group. Mean SF and iron saturation levels were also significantly higher in the IV Fe group.	The significant number of patients who withdrew from the study (20% from the IV Fe group and 36% from the oral iron group) is cause for some concern regardless of whether reasons for exclusion were unrelated to treatment. Such selection bias may have affected the data. Despite such concerns, this randomized trial provides persuasive evidence on the greater effectiveness of IV Fe dextran compared to oral iron therapy.

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Frankenfield D, Johnson C, Wish J, Rocco M, Madore F, Owen W / Anemia management of adult hemodialysis patients in the US: results from the 1997 ESRD Core Indicators Project / Kidney International / 2000	Epidemiological study	Hct, TSAT, SF, weekly EPO dose, serum albumin and iron prescription practices were assessed.	Analysis was conducted on the medical records of a random sampling of Medicare-eligible ESRD patients who were receiving in-center HD on 12/31/96. Patients who were not on EPO were excluded from analysis. Of a sample of 7292 patients, 4991 were included in the final analysis.	The mean Hct for the entire sample was 32.6% +/- 3.5%. 72% of patients had a Hct > 30%, while 42% had Hct between 33 - 36%. Mean SF level was 386 ng/ml +/- 422 ng/ml. 79% had levels greater than or equal to 100 ng/ml. 77% of patients were prescribed iron (in some form) at least once in the 3 month study. Only 54% patient were prescribed IV Fe.	Study highlights current status of hematological indicators of anemia within the Medicare ESRD population. The authors point out the need for better iron prescription practices, especially for IV Fe therapy.
Fudin R, Jaichenko J, Shostak A, Bennett M, Gotloid L / Correction of uremic iron deficiency anemia in hemodialyzed patients: a prospective study / Nephron / 1998	Randomized clinical trial	Hb, Hct, iron, TSAT and SF levels were assessed once a month during follow-up period to evaluate response to iron therapy. Initial iron storage was assessed by means of sternal bone marrow aspiration	48 anemic patients starting renal replacement therapy were randomized into 2 group. The first group received IV Fe gluconate (Ferrlecit) (n=24). The second group was divided further to receive either oral iron therapy (n=12) or no iron supplementation (n=12). 9 patients dropped out due to reasons unrelated to iron therapy. All 36 patients evaluated were determined to be iron deficient. No patients received EPO, blood transfusions, or iron supplementation for at least 1 year.	At the end of a 12 month follow-up, both patients not receiving IV Fe therapy and patients receiving oral iron showed no significant differences in blood Hb or TSAT levels from those observed at time zero. Patients on IV Fe showed significant improvements in Hb and TSAT levels after 12 and 26 months of follow-up (mean levels of 110 g/l +/- 9 g/l vs. a baseline of 36.4 g/l +/- 56.8 g/l). No patients in the IV Fe group required blood transfusions. Both the no iron and oral iron groups required transfusions.	This randomized clinical trial presents persuasive evidence that IV Fe therapy may be more effective in treating anemia in chronic uremia patients on HD then either no treatment or oral iron therapy. The small sample sizes may, however, bias the results.

Author / Title / Journal / Year	Type of Study	Outcomes Studied	Patient Characteristics	Results	HCFA Comments
Granolleras C, Oules R, Branger B, Fourcade J, Shaldon S / Iron supplementation of hemodialysis patients receiving recombinant human erythropoietin therapy / Erythropoietin: Molecular Physiology and Clinical Applications / 1993	Case series	EPO dose and Hct levels were compared as patients underwent IV Fe dextran therapy. SF, serum iron, and TSAT were also measured.	18 HD patients were studied. Patients were on EPO with a constant dose for at least 4 months. Hct were also constant between 30-35% for at least 4 months after attaining target value. Patients were studied in two phases: Phase 1: patients received 1 g of IV Fe if TSAT< 20% or SF<100 Phase 2: patients received 10 mg of IV Fe per dialysis session regardless of TSAT or SF unless levels were over 50% and 1000 respectively.	Phase 1 2 Hct.* 29% 31% EPO* 66 46 SF 321 654 TS 31% 33% * = $p < .05$	Authors did not explain the sequence of trial phases clearly. For example, the aggregate data points measured for mean Hct and EPO dose did not indicate the number of patients administered IV Fe during each phase. Authors did not indicate how much time elapsed between phases or baseline values. Study showed some positive results but the ambiguity of the protocols and the small sample size make it difficult to judge the reliability of the data.
Gupta A / Pathogenesis of anaphylactoid reactions to intravenous iron / American Journal of Kidney Diseases / 2000	Overview	Not a clinical trial.	Not a clinical trial.	Not a clinical trial.	Article is a letter which discussed the pathogenesis of acute adverse reactions to IV Fe. Author proposes an alternative explanation for the cause of anaphylactoid reactions to IV Fe. No direct clinical evidence is presented, however.

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Horl W, Dreyling K, Steinhauer H, Engelhardt R, Schollmeyer P / Iron status of dialysis patients under rhuEPO therapy / Contrib Nephrology / 1990	Overview	Not a clinical trial.	Not a clinical trial.	Not a clinical trial.	This article reviews the available literature on the effect of EPO therapy on the iron status of dialysis patients. The author concludes that patients should have a sufficient level of SF before starting on EPO and that every patients on dialysis should be treated with some form of iron supplementation if iron overload is not present.
Hussain R, Chishti S, Naqvi S / Experience of iron saccharate supplementation in haemodialysis patients treated with erythropoietin / Nephrology / 1998	Cohort study	Hb, Hct, TSAT, EPO dosage, and SF levels were monitored and compared as iron-replete patients underwent either oral iron therapy or IV Fe saccharate therapy for 3 months.	20 HD patients were enrolled into the study. Patients had Hb < 8.5 G/dl, normal folate and B12 level, SF between 200 and 800 ng/ml, and TSAT > 30%. Patients were split into 2 groups: Group 1 (n=10) were on IV Fe saccharate (100mg), Group 2 (n=10) were given oral Fe (60mg) 3 times a day. EPO therapy was also commenced on both groups. Dosage was adjusted according to Hb.	Group 1 2 Hb init. 7.8 8.0 end 11.6 10.5 p-val <0.001 <0.001 SF init. 386 446 end 671 367 p-val <0.05 =0.50 Target Hb (11-12 G/dl) was achieved in all Group 1 patients except one. Only 5 patients achieved target Hb levels in Group 2. EPO dose was increase in 1 patients from Group 1 and 6 patients in Group 2.	Study provides some evidence that iron-replete patients treated with IV Fe saccharate have a better response to EPO therapy compared to those on oral iron therapy. There is an issue with selection bias given that (1) the sample size (10 in each group) is quite small, and (2) patients were not randomized between the two treatment groups. However, authors' results are consistent with findings from other clinical studies.

Author / Title / Journal / Year	Type of Study	Outcomes Studied	Patient Characteristics	Results	HCFA Comments
Kooistra M, Niemantsverdriet E, Es A van, Mol-Beermann N, Struyvenberg A, Marx J / Iron absorption in erythropoietin-treated haemodialysis patients: effects of iron availability, inflammation and aluminum / Nephrology Dialysis Transplantation / 1998	Case-control study	Iron absorption and the effects of iron status, aluminum status, and inflammation were studied. TSAT were used as a measurement of iron availability for developing red blood cell. Group 1 (n=8) had TSAT levels below .20 and were designated functionally iron deficient. Group 2 (n=8) had TSAT levels above .20 and were designated as iron-replete. Iron absorption was measured via ingestion and activity of 59 Fe	20 clinically stable chronic HD patients were included. All patients had been treated with EPO for more than 6 months and had stable HCT between 30 to 35% for more than 4 weeks. Patients were given oral iron (with 59 Fe) during the first part of the study. The second part which was done 6 weeks later involved ingestion of the same oral iron supplement and an aluminum hydroxide. Iron absorption data was compared to historical data obtained from iron absorption database. 68 healthy controls were selected. In addition, 27 subjects with uncomplicated iron deficiency and Hct levels between .30 and .35 were all selected. 4 patients were excluded due to the following reasons: digestive tract bleeding, renal transplantation, equipment failure.	There were no significant difference between the two group based on iron metabolism parameters. Mucosal uptake and iron retention were both significantly higher in Group 1 compared to Group 2. Uptake, mucosal transfer, and retention were significantly lower in Group 1 compared to the healthy iron deficient controls. Uptake and retention were significantly lower in Group 2 compared to the normal healthy controls. After aluminum ingestion, Group 1 patients had significantly impaired uptake and iron retention. There were no significant effects to Group 2. There were no differences in iron absorption patterns between the two groups	In those patients taking oral iron therapy, this study presents persuasive evidence that the iron absorption rates of dialysis patients on EPO are significantly lower compared to healthy controls. This is true regardless of functional iron status. The small sample sizes (8 in each group) and use of historical controls may introduce important selection biases. The authors conclude that absorption of iron is significantly decreased in dialysis patients. What is not factored out is the cause: whether it is the actual dialysis or the use of EPO. Both factors can significantly stress the body's metabolism and regulation of iron

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Levin N, Cavallo G, Spinowitz B, et al / Safety of iron sucrose injection for iron deficiency in patient with anaphylaxis after iron dextran: preliminary results / Journal of the American Society of Nephrology / 1999	Case series	Review limited to full text, published articles.	Review limited to full text, published articles.	Review limited to full text, published articles.	The abstract does not contain sufficient evidence to thoroughly review and critique the clinical information and study protocols.
Ma J, Ebben J, Xia H, Collins A / Hematocrit levels and associated mortality in hemodialysis patients / Journal of the American Society of Nephrology / 1999	Ecological study	Primary endpoints of the study were all-cause death and cause specific death during the follow-up period. Patients were identified during the entry period and mortality risk was evaluated the next year from January 1 to December 31, 1994.	All prevalent Medicare HD patients surviving the entry period from July 1 to December 31, 1993 were included. Only patients with 4 or more EPO claims were included. Patients with Hct > 36% were excluded. Analysis was conducted on 75,283 patients.	Results show that patients with Hct < 30% had significantly higher risk of all-cause and cause-specific mortality compared to patients with Hct levels between 30% and 33% (12% - 33%). Without disease severity adjustment, patients with Hct between 33% and 36% had the lowest risk for all-cause and cardiac mortality.	Overall, increases in Hct levels are associated with improved patient survival. Study highlights the importance of anemia management in HD patients. Furthermore, study indicates an optimal target Hct range which may increase survival for ESRD patients.
Macdougall I / Strategies for iron supplementation: oral versus intravenous / Kidney International / 1999	Overview	Not a clinical trial.	Not a clinical trial.	Not a clinical trial.	This article reviews the various modes of iron supplementation: oral, intramuscular, IV. Author also reviews literature that compares the effectiveness of IV Fe to that of oral iron. The author concludes that IV supplementation is superior to either oral or intramuscular.

Author / Title / Journal / Year	Type of Study	Outcomes Studied	Patient Characteristics	Results	HCFA Comments
Macdougall I, Tucker B, Thompson J, et al / A randomized controlled study of iron supplementation in patients treated with erythropoietin / Kidney International / 1996	Randomized clinical trial	Hb response, SF, iron status, and EPO dosage were the principal endpoints.	38 iron-replete patients (SF 100-800 micrograms/L) with renal anemia who were starting EPO therapy were enrolled in the study. Doses for EPO were kept constant unless Hb levels increased to above 12 g/dl OR there were no significant increases in Hb levels after 8 weeks. Patients were randomized to either receive: IV Fe dextran (n=12), oral iron (n=13), or no iron supplementation (n=12). One patient was excluded due to anaphylactiod reaction.	The following is the EPO dosage adjustments for the 3 groups: IV Oral No Increase 1 3 6 Same 6 6 6 Decrease 5 4 0 * = statistical sign. ($p<0.05$) Hb response: IV Fe > oral * (by week 8) IV Fe > no iron * (by week 12) oral = no iron SF levels: IV Fe > oral * (by week 8) IV Fe > no iron * (by week 12) oral = no iron EPO dose/week: IV Fe < oral IV Fe < no iron * (by week 12) EPO total amount: IV Fe < oral IV Fe < no iron *	Though there is concern for the small sample sizes, this study provides persuasive evidence regarding the use of IV Fe therapy. The study shows improvements in Hb levels and EPO response in iron-replete patients on IV Fe therapy. The drop in SF levels in the oral and no iron groups suggests that these treatment modalities may be inadequate in maintaining sufficient iron stores. The authors note that this study is limited to the initiation of iron therapy and its effect on the hematopoietic response to EPO. One cannot generalize such data to the maintenance phase of treatment.
Mason N, Bailie G, Johnson C / Managing anemia with intravenous iron / For Patients Only / 2000	Overview	Not a clinical trial.	Not a clinical trial.	Not a clinical trial.	Article provides information on the etiology of iron deficiency, laboratory indicators for diagnosis, and IV Fe treatment options.

Author / Title / Journal / Year	Type of Study	Outcomes Studied	Patient Characteristics	Results	HCFA Comments
National Kidney Foundation Study Group / National Kidney Foundation-Dialysis Outcomes Quality Initiative clinical practice guidelines for the treatment of anemia of chronic renal failure: iron support / American Journal of Kidney Diseases / 1997	Overview	Not a clinical trial.	Not a clinical trial.	Not a clinical trial.	Article provides background material and guidelines on the need and use of iron-support therapy for ESRD patients.
Navarro J, Teruel J, Liano F, Marcen R, Ortuno J / Effectiveness of intravenous administration of Fe-Gluconate-Na complex to maintain adequate body iron stores in hemodialysis patients / American Journal of Nephrology / 1996	Case series	Patients' body iron stores were assessed after being treated with IV Fe gluconate (Ferrlecit) for 6 months. SF levels were used as a marker of body iron stores and iron requirements.	58 patients were enrolled in this protocol. 31 were excluded because of the following reasons: chronic hepatitis, chronic inflammatory diseases, intercurrent infection, external blood loss, blood transfusions required, variations in monthly Hb concentrations greater than or equal to 1 g/dl. 27 patients completed the study (16 of whom were on EPO therapy). Menstruating women were included in study.	In all cases, there were no significant variations in body iron stores and Hb levels remained stable. Patient were then classified into three groups based on whether their body iron stores (A) decreased, (B) remained stable, or (C) increased. There were statistical differences in basal body iron stores in these three groups according to SF levels: A= from 457 to 232 mg B= from 582 to 582 mg C= from 230 to 562 mg After excluding menstruating women, iron requirements in patients on EPO were similar to those not on EPO. There were no adverse reactions to the IV Fe supplement.	There was no comparison to a control group. Over one half of the patients enrolled were later excluded. In addition, the study's remaining sample size is quite small. The division of patients into even smaller groups (A=8, B=11, C=8) leads to concerns that selection bias may have affected the reliability of the results of the study. No relationships between health outcomes and body iron stores were reported.

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Nissenson A, Lindsay R, Swan S, Seligman P, Strobos J / Sodium ferric gluconate complex in sucrose is safe and effective in hemodialysis patients: North American clinical trial / American Journal of Kidney Diseases / 1999	Randomized clinical trial with matched controls	Hb, SF, iron saturation and Hct levels were monitored as patients received IV Fe gluconate (Ferrlecit).	88 chronic HD patients with either SF levels less than 100 ng/ml or iron saturation less than 18% AND either a Hb level less than 10 g/dl or Hct of 32% or less. EPO doses were required to remain unchanged throughout the study. Patients were randomized to receive IV Fe gluconate in one of two doses: high dose (n=44), 1 gram; or low dose (n=39), 0.5 grams. These patients were compared to matched control group (n=25) who were receiving only oral iron therapy and met the same entry criteria as the patients receiving IV iron	Mean increases from baseline of Hb in g/dl: Day 2 14 30 1g 1.0 1.1 1.3 0.5 g 0.3 0.3 0.5 oral 0.4 0.4 All values for the 1g group were significant compared to baseline. Only day 30 of the 0.5g group was significant. All values for the oral were insignificant. Mean increases from baseline of Hct in %: Day 2 14 30 1g 3.1 3.6 3.5 0.5 g 1.1 1.4 1.4 oral 0.8 0.4 All values for the 1g group were significant. Only day 14 and 30 of the 0.5g group were significant. No values for the oral were significant. Significant inter-group differences in Hb and Hct increases were only observed between the following: high dose vs. low dose, high dose vs. oral. Differences between low dose and oral were not significant.	Study suggests safety of IV Fe gluconate. The study demonstrates the greater efficiency of IV Fe gluconate over oral iron therapy. However, the short observation period may have affected the low success rates observed in the oral iron group.

Author / Title / Journal / Year	Type of Study	Outcomes Studied	Patient Characteristics	Results	HCFA Comments
Owen W Jr., Szczech L, Johnson C, Frankenfield D / National perspective on iron therapy as a clinical performance measure for maintenance hemodialysis patients / American Journal of Kidney Diseases / 1999	Overview	Not a clinical trial.	Not a clinical trial.	Not a clinical trial.	Article provides a persuasive argument on the use and mode of iron therapy as a clinical performance measure. Authors comment on the increased effectiveness of IV Fe and the reluctance providers have in using such treatments because of concerns regarding anaphylaxis.
Senger J, Weiss R / Hematologic and erythropoietin responses to iron dextran in the hemodialysis environment / ANNA Journal / 1996	Case series	EPO doses, SF, TSAT, Hct levels were monitored during treatment with IV Fe dextran. Target values were Hct of 33%, SF < 1000 ng/ml, and a statistically significant reduction in EPO dose. EPO doses were adjusted according to increases in Hct to be consistent with target goals.	13 clinically stable HD patients were enrolled into the study. Patients selected had been on HD for at least 4 months and a TSAT < 20% and/or SF < 1000 ng/ml. Oral iron was given to all patients to bolster iron stores. Patients receiving blood transfusions, not taking EPO, or have chronic inflammatory processes were excluded. 2 patients died of chronic renal failure and 2 others broke protocols to receive care elsewhere.	Data points were available for all 13 patients up until 6 months. Data from 11 patients were available at 9 months and 9 patients at 12 months. EPO: Mean EPO dose was significantly reduced by 77% (by 3100 units per patient) after 6 months. Hct: There was an 8% increase from baseline values at 6 months. TSAT & SF: Mean values increased by 65% and 78% respectively.	Study provides some evidence regarding the effect of IV Fe dextran use on EPO dosage requirements, Hct, TSAT, and SF. Sample size is quite small and there is no comparison to oral iron treatment. Authors do not comment on the use of oral iron prior to IV Fe administration. However, results seem to be fairly consistent with those found in other studies.

Author / Title / Journal / Year	Type of Study	Outcomes Studied	Patient Characteristics	Results	HCFA Comments
Silva J, Andrade S, Ventura H, et al / Iron supplementation in haemodialysis--practical clinical guidelines / Nephrology Dialysis Transplantation / 1998	Cohort study	TSAT, hypochromic erythrocytes, Hb, SF, EPO dosage, and serum iron levels were monitored as patients were treated with IV Fe sucrose. An increase of 1 g/dl of Hb over initial value was considered a positive response to treatment and indicative of iron deficiency.	33 HD patients on EPO were selected from a dialysis unit who had met at least one of the following entry criteria: TSAT<20%, hypochromic erythrocytes > 10%, or SF < 400. 20 patients were on oral iron prior to the study. Patients were divided into 2 groups based on SF levels at baseline: Group 1 = SF< 100 (n=17), Group 2 = 100<SF<400 (n=16). Patients were excluded if they had active inflammatory or infection disease, hematological disease, psychosis, iron overload, need of blood transfusion, or change in renal replacement treatment	Iron deficiency was diagnosed in 29 of the 33 patients. There was a progressive increase in mean Hb level (10.8 at baseline vs. 12.8 at 6 months [p<0.0001]). There was a progressive increase in mean SF level (137 at baseline vs. 456 at 6 months [p=0.0001]). A plateau effect was observed between the 4th and 6th month. EPO use decrease significantly by 28% (6871 at baseline vs. 4947 at 6 months [p<0.003]. There were no significant differences in Hb and hypochromic erythrocytes levels between the 2 groups. SF levels were significantly lower in Group 1 throughout the study. Serum iron and TSAT were similar in both groups at baseline but became significantly higher in Group 1 at the end. Group 1 required a lower dose of EPO throughout the study.	Regardless of SF levels, a significant portion of the study population was diagnosed as iron deficient. This indicates either that SF values alone are insufficient in diagnosing iron deficiency or the cutoff of 400 is not adequate enough to indicate iron deficiency in HD patients. Both groups responded to treatment. Although there was no comparison to a control group, the evidence presented demonstrates the effectiveness of IV Fe therapy in HD patients, findings consistent with other studies.

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Silverberg D, Blum M, Peer G, Kaplan E, Iaina A / Intravenous ferric saccharate as an iron supplement in dialysis patients / Nephron / 1996	Cohort study	Hct, EPO dosage, SF and iron saturation were monitored for 12 months as patients underwent IV Fe saccharate therapy.	73 patients on chronic dialysis (64 on HD, 9 on CAPD) were enrolled into the study. Patients had no signs of infection or gastrointestinal bleeding. Oral iron was not used either before or during the study. All patients were receiving phosphate binders. Patients were divided into five groups. HD patients: Group 1: IV Fe added in patients already taking EPO. Group 2: IV Fe and EPO started simultaneously. Group 3: IV Fe without EPO. CAPD patients: Group 4: Taking IV Fe and EPO Group 5: Taking IV Fe without EPO	EPO Hct SF Grp 1 int. 98.8 28.7 99.0 0-6 98.8 33.7* 402.7* 6-12 38.4* 33.6* 383.3* Grp 2 int. 0 28.1 83.7 0-6 95.6 34.1* 369.9* 6-12 23.2* 33.9* 348.8* EPO Hct SF Grp 3 int. 0 30.5 49.0 0-6 0 37.5* 293.8* 6-12 0 37.9* 287.8* Grp 4 int. 61.4 28.4 102.8 0-6 61.4 33.3* 470.5* Grp 5 int. 0 27.7 144.6 0-6 0 35.6* 459.9* * = $p < 0.05$ vs. int.	The study provides good evidence on the effect of IV Fe therapy on Hct, EPO dose, and SF levels. Furthermore, the data highlights the effectiveness of IV Fe even in patients who are not undergoing EPO treatment. However, the sample sizes for each of the groups were quite small and inconsistent. Patients were also not randomized into their respective groups. Both points can introduce selection bias.

Author / Title / Journal / Year	Type of Study	Outcomes Studied	Patient Characteristics	Results	HCFA Comments
Silverberg D, Iaina A, Peer G, et al / Intravenous iron supplementation for the treatment of the anemia of moderate to severe chronic renal failure patients not receiving dialysis / American Journal of Kidney Diseases / 1996	Case series	Serum creatine, creatine clearance, Hct, Hb, SF, iron, and TIBC levels were monitored as patients underwent IV Fe sucrose therapy.	33 patients with moderate to severe chronic renal failure were enrolled into the study. These patients were not receiving dialysis. 32 patients in the sample were hypertensive and undergoing treatment to control their blood pressure. All had Hb < 11.0 g/dl, been followed for at least 6 months prior to the study, and had been receiving oral iron supplements. No patient had previously been on EPO. Patients were followed on IV Fe sucrose for 5 months.	One patient was not included in the study because of an adverse reaction to the initial test dose. By the end of the study (6 months) mean Hct and Hb levels increased by 19.% +/- 3.8% (p=0.035) and 0.6 +/- 1.2 g/dl (p=0.008) respectively. SF and iron saturation levels increased steadily as well (statistically significant). 22 patients (66.7%) experienced increases in Hb and Hct and were considered responders. 11 patients had decreases in Hb and Hct and were considered non-responders.	Study provides some evidence on the effectiveness of IV Fe sucrose in pre-dialysis patients. Though there is no comparison with other modes of iron treatment (oral iron or no iron), the results are fairly consistent with those found in other studies. It should be noted however, that nearly 1/3 of the study population did not respond to IV Fe treatment (there were no significant differences existed between responders and nonresponders). This illustrates the lack of predictability regarding which patients will respond to IV Fe therapy.
Suh H, Wadhwa N / Iron dextran treatment in peritoneal dialysis patients on erythropoietin / Advances in Peritoneal Dialysis / 1992	Case series	SF, TIBC, blood count, reticulocyte count, serum iron, Hct, EPO dose and TSAT were monitored as peritoneal dialysis patients underwent IV Fe dextran treatment.	7 stable ESRD patients were studied (6 on CAPD, 1 on continuous cycling peritoneal dialysis [CCPD]). Patients were started on IV Fe dextran because of poor response to EPO and/or oral iron. 6 patients received EPO and 1 was on decadurabolin. There were no signs of gastrointestinal bleeding, hyperparathyroidism, or aluminum toxicity.	Mean duration of IV Fe therapy was 7 months. Mean dose of EPO was reduced significantly (119 to 87) five months into the study. Hct increased significantly (29% to 38%). SF levels increased significantly (267 to 660).	Study provides some evidence on the efficacy of IV Fe dextran in peritoneal dialysis patients. However the sample is quite small (n=7) and there is no comparison with other modes of iron treatment (oral iron or no iron).

Author / Title / Journal / Year	Type of Study	Outcomes Studied	Patient Characteristics	Results	HCFA Comments
Sunder-Plassmann G, Horl W / Comparative look at intravenous iron agents: pharmacology, efficacy, and safety of iron dextran, iron saccharate, and ferric gluconate / Seminars In Dialysis / 1999	Overview	Not a clinical trial.	Not a clinical trial.	Not a clinical trial.	Article provides a comparative review of the available literature on the safety, toxicity, pharmacology, and clinical effectiveness of three IV Fe agents: iron dextran, iron sucrose, and iron gluconate.
Tarng DC, Huang TP, Chen TW / Mathematical approach for estimating iron needs in hemodialysis patients on erythropoietin therapy / American Journal of Nephrology / 1997	Cohort study	Hb, Hct, SF and other iron metabolism parameters were measured regularly for 6 months. The main purpose of the study was to predict iron needs from Hb and SF levels and establish a formula that determines iron needs in patients with functional iron deficiency.	40 HD patients were enrolled into the study. Patients has an initial Hct > 25%. All patients has basal SF levels > 100. Patients were divided into 2 groups according to TSAT levels. Group 1 (n=20) had TSAT > or = 25% (not having functional iron deficiency), Group 2 (n=20) had TSAT < 25% (having functional iron deficiency). EPO was administered to both groups. Group 2 patients also received IV Fe sucrose.	EPO dose increased significantly in both groups as compared to initial dose. At the end of the study, patients had a mean dose of 92 unit/kg/wk (Group 1) and 90 unit/kg/wk (Group 2). At 6 months, mean Hb were significantly elevated in both groups as compared to baseline. Mean SF significantly declined in Group 1 and significantly increased in Group 2. There was no significant change in TSAT in Group 1. Group 2 had a significant increase in TSAT. At the end of the study 18 patient in each group (90%) had TSAT > 25%.	Study is more designed to develop a mathematical methodology for assessing iron needs in HD patients on EPO. The division of patients according to TSAT levels and the administration of IV Fe sucrose to only the functional iron deficient group makes it difficult to extrapolate any conclusions regarding comparable effectiveness of IV Fe therapy. It is interesting to note that the iron-replete group with TSAT > 25% (which did not receive iron supplementation) still experienced a significant decline in iron stores.

Author / Title / Journal / Year	Type of Study	Outcomes Studied	Patient Characteristics	Results	HCFA Comments
Taylor JE, Peat N, Porter C, Morgan AG / Regular low-dose intravenous iron therapy improves response to erythropoietin in hemodialysis patients / Nephrology Dialysis Transplantation / 1998	Case series	Patients' Hb, SF, EPO dose, and IV Fe doses were measured at 6-weekly intervals over a 6-month period.	46 HD patients were given IV Fe gluconate (Ferrlecit). All were receiving EPO solely due to renal failure and had a stable dose for at least 3 months. Patients were divided into low SF (<100) and normal SF (>100) groups according to levels at the start of the study. EPO doses were adjusted in order to maintain Hb levels of 11-13 g/dl for men and 10-12 g/dl for women.	Median results for low SF group (n=12): Pre Post SF 68 210.5 Hb 10.05 11.0 EPO 9000 6000 Median results for normal SF group (n=34): Pre Post SF 176 304.5 Hb 9.85 11.25 EPO 6000 4000 All increments were significant.	The study does not compare patients results to a control group (i.e. oral iron or no iron). The study provides good evidence that regular low-dose IV Fe therapy could improve response to EPO therapy in patients with normal or low body iron stores. Proper iron supplementation could lead to reductions EPO dosage requirements.

Author / Title / Journal / Year	Type of Study	Outcomes Studied	Patient Characteristics	Results	HCFA Comments
Wingard R, Parker R, Ismail N, Hakim R / Efficacy of oral iron therapy in patients receiving recombinant human erythropoietin / American Journal of Kidney Diseases / 1995	Randomized clinical trial	Study assesses the comparative efficacy of four types of commonly used oral iron preparations. Outcome parameters measured included serum iron, TSAT, SF, EPO dosage, and Hct levels. Patient compliance was also monitored.	Patients were eligible if they met the entry criteria: (1) on chronic HD > 3 months, (2) on EPO > 6 months, (3) require oral iron to main Hct > 25%, (4) no active gastrointestinal blood loss in the last month, (5) no gastrointestinal malabsorption syndrome, (6) no acute inflammation or infection, (7) no hospitalization in past 4 weeks. 46 patients were enrolled in protocols and randomized into one of the following 4 groups: Chromagen, Feosol, Niferex, or Tabron. All patients were prescribed with (1) a total dose of iron = 200mg/day, (2) 100 mg of ascorbic acid. 37 patients completed the study protocols.	There were no significant differences in outcome parameters at baseline. At the end of the follow-up period of 6 months, there were no significant changes in serum iron and TSAT in any study group. SF decreased substantially in Chromagen, Niferex, and Fersol groups, and minimally in the Tabron group. All groups were able to maintain and increase mean Hct levels (with statistical significance in the Chromagen, Feosol, and Tabron groups). Mean EPO doses decreased in all groups except the Chromagen group.	This study provides solid evidence on the comparative efficacy of oral iron preparations. The authors state that oral iron can improve Hct levels and reduce EPO levels for six months. However, because SF levels simultaneously decreased, authors conclude that, even with high compliance to oral, at some point IV Fe would have to be used to replete iron stores. The Tabron group had the advantage, though there were no statistically significant advantages of one iron preparation over the others. Study, however, did not compare oral iron to an IV Fe agent. Conclusions about the need for IV Fe beyond the 6 month follow-up period were not confirmed. Study could have benefited from a longer follow-up period.
Wyck van D, Al-Saloum M, Charytan C, Hafeez T, Levin N / Efficacy of iron sucrose injection for iron deficiency in patients with dialysis-associated anemia: preliminary results / Journal of the American Society of Nephrology / 1999		Review limited to full text, published articles.	Review limited to full text, published articles.	Review limited to full text, published articles.	The abstract does not contain sufficient evidence to thoroughly review and critique the clinical information and study protocols.

Author / Title / Journal / Year	Type of Study	Outcomes Studied	Patient Characteristics	Results	HCFA Comments
Xia H, Ebben J, Ma J, Collins A / Hematocrit levels and hospitalization risks in hemodialysis patients / Journal of the American Society of Nephrology / 1999	Ecological study	Primary endpoints of the study were first hospitalization, cause-specific hospitalization, and multiple hospitalization during the follow-up period. Patients were identified during the entry period and risk for hospitalization was evaluated the next year from January 1 to December 31, 1994.	All prevalent Medicare HD patients surviving the entry period from July 1 to December 31, 1993 were included. Only patients on EPO were include since EPO claims require reporting of Hct levels. Analysis was conducted on 71,717 patients.	Results show that patients with Hct < 30% had significantly higher risk of hospitalization compared to patients with Hct between 30% and 33% (14% - 30% without disease severity adjustment, 7% - 18% with disease severity adjustment). Patients with Hct between 33% and 36% had the lowest risk for hospitalization, with or without adjustment.	Study highlights the importance of anemia management in HD patients. Furthermore, study indicates an optimal target Hct range which may reduce hospitalization and increase survival for ESRD patients.